PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

VOSSIUS & PARTNER
Siebertstrasse 4
81675 München
ALLEMAGNE

EINGEGANGEN
Vossius & Partner
09. Aug. 2001
Frist bearb.: 7.11. 7.10. G

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	07.08.2001
Applicant's or agent's file reference: D 2145 PCT /1	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/08570	01/09/2000	10/09/1999

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68

Applicant
EPIDAUROS BIOTECHNOLOGIE AG et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☒	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 10/01/2002.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Bradbrook, D

Formalities officer (incl. extension of time limits)
Digiusto, M
Telephone No. +49 89 2399 8162

Express Mail Label
No. EV 045436952 US

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-48 as originally filed

Claims, No.:

1-43 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

Sequence listing part of the description, pages:

1-41, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-12,14-32,35-43(in part); 13,33,34(in full),

because:

   ☒ the said international application, or the said claims Nos. 28,29,31,32 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 13 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-32,35-43(in part); 33,34(in full).

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.
   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	31,32,42,43 (NO)
Inventive step (IS)	Claims	1-12,14-30,35-41 (NO)
Industrial applicability (IA)	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Section I Basis of the opinion

1. Sequence listing pages 1-41 are numbered 49-89.

Section III Non-establishment of opinion

1. As a consequence of the objections expressed in the International Search Report with respect to lack of clarity of claims 1 and 37, examination of specifically identified sequences is restricted thus:
   in claim 1: SEQ ID NOs 54, 55, 129;
   in claim 37: SEQ ID NOs 15, 16, 30, 31, 54, 55, 124, 125, 140, 141.

2. No opinion with respect to the provisions of Article 33(1) PCT is given for the following claim as it fails to meet the requirements of Article 6 PCT to the extent that any opinion would be meaningless: claim 13 is defined only in functional terms, so that the claimed nucleic acid is not properly defined.

3. Claims 28, 29, 31 and 32 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V Reasoned statement

1. Reference is made to the following documents:

   D1: Westlind et al., Biochem.Biophys.Res.Comm., Vol.259, pp.201-205 (27.05.99);
   D2: WO-A-99 13106 (Axys Pharm.Inc.; 18.03.99).

2. Novelty (Article 33(2) PCT) and inventive step (Article 33(3) PCT)

a. Claims 31 and 32 are not novel prima facie because they relate only to the disorder rather than to the cause. Thus, the claim is prejudiced by a method for preparing any drug for treating cancer. Similarly, the subject-matter of claims 42

and 43 is not restricted to disorders or cancers which are caused by any of the polymorphisms of the invention. Therefore, said claims are also prima facie not novel.

b. The present invention is based on the discovery of two polymorphisms: in the CYP3A4 gene, a G/A substitution in exon 3 at nucleotide position 6004, giving rise to an amino acid substitution of Gly / Asp in the protein; in the CYP3A7 gene, a C or G in exon 11 at position 1229, giving Thr / Arg in the protein.

c. Neither of these polymorphisms is identified in the prior art. Therefore, the subject-matter of claims 1-12, 14-30 and 35-41, insofar as searched and examined, appears to be novel.

d. However, the mere discovery of a polymorphism in a known gene is not in itself inventive: polymorphisms are widespread throughout the human genome, and have been identified previously in the CYP3A4 gene (cf D1 and D2). The identification of another polymorphism without the demonstration of an unexpected technical effect of the polymorphism would not appear to solve a technical problem. It is disclosed in the application that the G6004A substitution in the CYP3A4 gene results in altered activity of the encoded enzyme (cf p.38-39: bridging paragraph); however, the implications of this for a subject carrying the altered enzyme appear not to have been addressed. As such, knowledge of the existence of the altered enzyme in some individuals does not appear to solve a problem, particularly with respect to diagnosis or treatment of disease. Moreover, there is no indication in the application as to the effect of the T1229R polymorphism on the functioning of the CYP3A7 protein. As no effect has been identified, it appears that no problem is solved.

e. Therefore, claims 1-12, 14-30 and 35-41 appear not to be inventive.

3. Industrial applicability (Article 33(4) PCT)

For the assessment of the present claims 28, 29, 31, 32, 42 and 43 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation

of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VI Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-00 24926	04.05.00	22.10.99	23.10.98*

*priority not checked

1. The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above document would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT). Furthermore, should the present application enter the national or regional phase, the above document could be relevant to the question of novelty.

Section VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

Section VIII

1. The following objections are under Article 6 PCT:

a. Claim 3 relates to a result to be achieved, viz the expected effect of polymorphisms in a gene; in this case the subject-matter should be defined by the polymorphisms which cause the required effect.

b. Claims 15-17: claimed transgenic animal may naturally contain one of the polynucleotides of claims 1-3, i.e. said claims are not restricted to animals in

which the introduced gene is one of those of the present invention.

c. Claims which rely on a causative association between the polymorphisms and a disease are speculative as there is no support in the application for such. Moreover, such claims are not properly disclosed, contrary to the requirements of Article 5 PCT.